PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
05558.0011.00PC00		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/010346	01.04.2004	01.04.2003

International Patent Classification (IPC) or national classification and IPC
A61K45/00, A61K31/505, A61K31/519

Applicant
APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.01.2005	08.07.2005
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/010346

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-63	as originally filed
Claims, Numbers	
1-19, 39-66	as originally filed
20-38	received on 26.01.2005 with letter of 26.01.2005
Drawings, Sheets	
1/14-14/14	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 20-60

because:

☒ the said international application, or the said claims Nos. 20-60 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/010346

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-66
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-66
Industrial applicability (IA)	Yes:	Claims	1-19,61-66
	No:	Claims	20-60 see item III below

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

For the assessment of the present claims 20 to 60 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:
D1: US2002/0065324

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 66 is not new in the sense of Article 33(2) PCT.

D1 discloses methods of inducing ovulation in a female host comprising the administration of a non-polypeptide cyclic adenosine monophosphate (cAMP) level modulator to the female host, in particular specific administration of the phosphodiesterase inhibitor prior to the luteal phase of the host's ovulatory cycle. Preferred non-polypeptide cAMP level modulator include phosphodiesterase inhibitors, particularly inhibitors of phosphodiesterase 4 isoforms.
In particular example 3 relates to the effect of the PDE Inhibitor on ovulation in the presence of a subeffective dose of hCG in vivo. Example 2 relates to the effect of PDE

inhibitor compound 1 on follicle maturation, in vivo. Examples 4 to 9 relate respectively to the effect of several PDE inhibitors on ovulation and fertility.

This teaching anticipates the subject-matter of claims 1 to 66.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 66 does not involve an inventive step in the sense of Article 33(3) PCT over the teaching of D1

Re Item VI

Certain documents cited

The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the documents WO-A-03051344 and US2004/0029891 cited in the international search report could become relevant to assess whether claims 1 to 66 satisfy the criteria set forth in Article 33(1) PCT.

Re Item VIII

Certain observation on the clarity of the claims:

Claims 1 to 19 are not clear, contrary to article 6 PCT, since the claims are not drafted in a second medical form, since the disease to be treated is not specified. In claims 7 and following the claims are concerned with a dosage regimen.

20. A method of increasing follicle maturation comprising treating a female with a composition comprising a phosphodiesterase (PDE) inhibitor in an amount effective to stimulate follicular maturation.

21. A method of increasing oocyte maturation comprising treating an oocyte *in vitro* with a composition comprising a PDE inhibitor in an amount effective to cause oocyte maturation.

22. A method according to claim 20, wherein the composition comprises at least one PDE 4 inhibitor.

23. A method according to claim 20, wherein the composition comprises at least one PDE 4 inhibitor selected from the group consisting of Piclamilast, Roflumilast, Ariflo, Filaminast, Mesopram, D4418, Arofylline, and CL1044.

24. A method according to claim 20, wherein the composition comprises at least one PDE 4 inhibitor and one other PDE inhibitor selected from the group consisting of a PDE 1 inhibitor, a PDE 7 inhibitor, a PDE 9 inhibitor, a PDE 10 inhibitor, and a PDE 11 inhibitor.

25. A method according to claim 20 or 21, wherein the method further comprises treatment with at least one gonadotropin selected from the group consisting of FSH, luteinizing hormone, and chorionic gonadotropin.

26. A method according to claim 22, wherein the method further comprises treatment with at least one gonadotropin selected from the group consisting of FSH, luteinizing hormone, and chorionic gonadotropin.

27. A method according to claim 23, wherein the method further comprises treatment with at least one gonadotropin selected from the group consisting of FSH, luteinizing hormone, and chorionic gonadotropin.

28. A method according to claim 24, wherein the method further comprises treatment with at least one gonadotropin selected from the group consisting of FSH, luteinizing hormone, and chorionic gonadotropin.

29. A method according to claim 20 or 21, wherein the method further comprises treatment with FSH.

30. A method according to claim 20 or 21, wherein the method further comprises administering FSH and at least one non-FSH gonadotropin hormone.

31. A method according to claim 30, wherein the non-FSH gonadotropin hormone is luteinizing hormone.

32. A method according to claim 30, wherein the non-FSH gonadotropin hormone is chorionic gonadotropin.

33. A method according to claim 20, wherein the method comprises administering a stimulator, agonist or adjuvant of FSH alone in combination with a PDE 4 inhibitor.

34. A method according to claim 33, wherein the stimulator of FSH is selected from the group consisting of Letrozole, Anastrozole, and Vorozole.

35. A method according to claim 25, wherein the PDE inhibitor and the gonadotropin hormone are administered concurrently.

36. A method according to claim 25, wherein the PDE 4 inhibitor and FSH are contained in a single vial as a mixture.

37. A vial containing a single dose of a mixture of PDE 4 inhibitor and FSH.

38. A method according to claim 25, wherein the PDE inhibitor is administered prior to the gonadotropin hormone treatment.